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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,645	07/12/2001	Yuri Kolesnikov	62072(51590)	3048

7590 01/18/2006

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,645	KOLESNIKOV ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,14,15 and 19-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-9,14,15 and 19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of applicants' amendments and remarks submitted October 3, 2005 is acknowledged.

Claim rejections 35 U.S.C. 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1, 7-9, 14-15, 19-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new Mater rejection. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

3. The limitations "not to central receptors" in claim 1; "not central or systemic analgesia" in claim 9; "not central receptors" in claim 15; "not to central opiate receptors" in claim 23; and "not to central opiate receptors" in claim 27 do not find support in the application as originally filed. It is noted that said limitations were not in the claims as originally filed. It is further noted that the specification, on page 9, indicated only that a topical formulation of the invention "is not required to deliver active ingredients in the topical formulation to central (brain and spinal cord) opiate receptors." This teaching does not support a limitation wherein the topical formulation is precluded from delivering the active ingredients centrally or systemically.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 9, 14, 15, 19-23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh (USPN 5849761) in view of Mayer et al. (USPN 5840731).

6. Yaksh teaches methods and compositions for the treatment of peripheral hyperalgesia (Abstract). Topical compositions comprising opiates are taught for local administration without eliciting CNS side effects (i.e. those caused by activation of the central receptors) (Abstract). Peripheral use of opiates, such as morphine, is taught as known in the art (col. 3, line 58-col. 4, line 9). The disadvantage of the use of morphine in the topical compositions disclosed by Yaksh is that it is taught to have short duration of activity and to have systemic and CNS side effects when used at high levels (col. 3, line 58-col. 4, line 9). formulated in creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, Effective concentrations of hyperalgesic compounds are bandages, etc. (col. 41, lines 7-12). Alkyl esters of fatty acids, propylene glycol and lecithin are disclosed as excipients for lotions (col. 42, lines 47-50., col. 43, line 50; col. 44, line 1). Aqueous solutions are taught (col. 44, lines 51-63). Yaksh does not specifically disclose a topical composition/method comprising morphine, nor does Yaksh specifically teach an NMDA

receptor antagonist. Yaksh does not specifically teach the concentration required to limit the morphine effect to a peripheral effect.

7. Mayer et al. teaches that the analgesic effectiveness of a combination drug composition comprising at least one analgesic is significantly enhanced by the addition of an NMDA receptor antagonist (Abstract). Mayer et al. teaches compositions comprising a first analgesic, a second component, and an analgesia-enhancing amount of an NMDA receptor antagonist and methods of treatment for alleviating pain by the administration thereof (col. 1, lines 6-27; col. 2, lines 30-coI. 3, line 5; col. 4, line 67-col. 5, line 13). Analgesics are taught to be selected from fentanyl, morphine, etc. (col. 3, lines 57-65). NMDA receptor antagonists are taught to be selected from ketamine, etc. (col. 4, lines 33-50). Excipients such as condensation products of ethylene oxide are also taught (col. 5, line 14-col. 6, line 11). Administration is taught to be achieved orally, rectally, intravenously, intramuscularly, subcutaneously, intrathecally, epidurally, or intracerebroventricularly (col. 4, line 66-col. 5, line 3). It is also noted that the composition of Example 1 comprises about 4% of an opioid analgesic (codeine phosphate).

8. It would have been obvious to one of ordinary skill in the ad to formulate a topical composition, as instantly claimed, comprising morphine and ketamine for only peripheral use because (1) Yaksh teaches that the formulation of morphine for only peripheral use is known in the art when the concentrations are sufficiently low; and (2) Mayer et al. teaches that the addition of an NMDA receptor antagonist (e.g. ketamine) to an analgesic composition is known in the art to significantly enhance the analgesia provided thereby. One would have been motivated to prepare and utilize such a composition because of an expectation of success in providing a topical composition suitable for peripheral relief with significantly enhanced analgesic effects, as

taught by Mayer et al., at a concentration low enough to avoid the systemic and CNS side effects of morphine taught by Yaksh.

9. Furthermore it would have been obvious to one of ordinary skill in the art at the time of the invention to arrive at a composition comprising the claimed amount of morphine because Yaksh teaches that it is known in the art that the concentration of morphine must be sufficiently low to avoid systemic and CNS side effects. It would have been obvious to the skilled artisan to optimize the concentration of morphine in the composition in order to avoid systemic or central delivery because "where the general conditions of a claim are disclosed in the prior ad, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

10. Claims 7, 8, 24, 25, 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yaksh and Mayer et al. as applied to claims 1, 9, 14, 15, 19-23, 26 and 27 above, and further in view of Mackles et al. (USPN 5322683).

11. Yaksh and Mayer et al. apply as disclosed above. The references lack the teaching of a local anesthetic.

12. Mackles et al. teaches that lidocaine is a topical analgesic (col. 3, lines 16-18).

13. It would have been obvious to one' of ordinary skill in the art at the time of the invention to add the lidocaine of Mackles et al. to the composition of the combined reference because (1) the combined references teach a topical analgesic composition; (2) Mayer et al. teaches the use of a second analgesic', and (3) Mackles et 41. teaches that lidocaine is a topical analgesic. One of ordinary skill in the art would have been motivated by an expectation of success in providing a second analgesic in further alleviating pain, as taught by Mayer et al.

Response to Arguments

14. Applicant's arguments submitted October 3, 2005 have been fully considered, but are not persuasive.

15. With respect to the new matter rejection, applicants contend that the application provide support for the limitations "not to central receptors" in claim 1; "not central or systemic analgesia" in claim 9; "not central receptors" in claim 15; "not to central opiate receptors" in claim 23; and "not to central opiate receptors" in claim 27, citing, as example, of page 15, line 13-19 and page 20, lines 1-10 and lines 23-25. The examiner found the arguments unconvincing. The claims as currently pending appear requiring that the composition herein, when applied topically to any mammal, including human, will ***not reach*** the central opiate receptors, or with no (zero) effect on central opiate receptors. The application as originally filed provides no support for such limitaiotn. Page 15, line 13-19, merely state that topical application may avoid ***profound*** psychomimetics effects, and provide no support for completely avoid any psychomimetics effects. page 20, lines 1-10 and lines 23-25 limited to a specific mammal (rat) in a specific skin area (tail), and would not support for all mammal, and for any topical application.

16. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

17. Applicants assert that Yaksh teaches away from the use of "conventional opioids" in the periphery because Yaksh specifically states that conventional opioids unsuitable for local application. The arguments are unpersuasive. As stated above, the cited references should have

been considered as a whole. Yaksh disclosed that peripheral use of opiates, such as morphine, is taught as known in the art, but have some disadvantage, particularly, because of "possibly can, if ***applied at sufficient levels***, have effects upon consciousness and respiration. This possible systemic effect, CNS effects and abuse potential render conventional opioid unsuitable for local application." Mayer's teaching have just addressed the issues concerned in the art, i.e., reduce the effective dosage of opioids, and thereby avoid the possible abuse potential. Therefore, one of ordinary skill in the art, at the time the claimed invention was made, would have been motivated to combine the teaching of Yaksh and Mayer and modify the known opioid topical composition according to Mayer to ovoid the possible abuse potential. Mayer provides solution to overcome the obstacle for topical application of opioid analgesics. Further, it is noted that Mayer teaches that "All modes of administrations are contemplated for" the combination of opioid and NMDA receptor antagonist. See, column 4, lines 66-67. Therefore, considering the cited prior art as whole, one of ordinary skill in the art would have been motivated to make and use a topical composition comprising an opioid analgesics and an NMDA receptor antagonist.

18. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER
Shengjun Wang
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Art Unit 1617

1.